Chemical Legacy

Contamination of the Child

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GREENPEACE

We are guilty of many errors and faults, but our worst crime is abandoning the children, neglecting the foundation of life. Many of the things we need can wait. The child cannot. Right now is the time his bones are being formed, his blood is being made and his senses are being developed. To him we cannot answer 'Tomorrow'. His name is 'Today'.
Gabriela Mistral,
1945 Nobel Prize Winner for Literature

This stuff is everywhere.
John Jake Ryan,
Health Canada, Ottawa, 2001

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Preface

In writing *Chemical Legacy: Contamination of the Child,* Dr Dorey has performed a considerable service. Children's health is clearly an emotive topic, but this is a scholarly report of the current state of knowledge about the contamination of the human species by a restricted list of chemical pollutants. The data come from reputable published sources, primarily peer-reviewed journals and government publications. The interpretation of the findings is guarded and dispassionate. This publication will serve as a useful literature review.

To set the report in context, I welcome the opportunity to discuss some aspects of environmental pollution and child health.

Evolution

Throughout evolution, organisms have, by chance mutations, produced a succession of novel compounds that have improved their own survival prospects at the expense of other species. An excellent example is penicillin, produced by yeasts to inhibit bacteria. Thus the 'chemical warfare' concept in nature throughout evolution is not a new one. However, when such changes occur, they do so on a very local basis and in low volume. Furthermore, the target species either adapts or succumbs to the new threat. The adaptation is usually realised by a progressively increasing ability of the target species to metabolise and detoxify the novel compound. In higher creatures, such as mammals, this process might be expected to occur over hundreds of generations.

During the past few decades, the human race, through its industries, has managed to disperse high volumes of many novel chemical pollutants throughout the biosphere at concentrations high enough to cause adverse biological effects.

It should come as no surprise to discover that some manufactured chemical compounds, many of which are surprisingly similar in structure to natural hormones, interfere with the chemical signalling systems within our own bodies. The control of development in the foetus and infant is very much under the control of hormones which are active in low levels of parts per trillion. This is within the range of environmental concentrations found for many environmental pollutants within the general population.

Toxicology

The mixture of chemicals that is found in the average person is extremely complex, in the toxicological sense. There are hundreds of groups of chemicals to be found within most people in the general population. Furthermore, within each group of organic chemicals there are usually many variants. For example, consider the pesticide toxaphene: there are over 60,000 congeners and enantiomers (mirror image molecules) possible from that single chemical group (Liem & Theelen, 1997; Vetter & Luckas, 1995; Vetter & Scherer, 1998). Then, in addition, there are metabolites to add to the complexity.

The realistic bottom line is that we are being exposed to tens of thousands of chemicals which simply didn't exist on this planet until a few decades ago. When our grandparents were in their mothers' wombs they would not have been exposed to these novel chemicals.

We have no tools for analysing the toxicity of the complex mixture to which we are exposed (Howard, 1997; Lang, 1995). Most toxicology is performed on chemicals one at a time. We have difficulty comparing chemicals even in combinations of pairs (Axelrad et al., 2002 and 2003). When we consider combinations of hundreds or thousands of chemicals, it is clear that we have not yet developed any methods that will allow for their rigorous toxicological analysis.

There is no indication of any imminent major breakthrough to this testing problem. That leaves us with only a generalised approach to safety through hazard reduction, i.e. reduction in exposure, using a precautionary approach. There are simply no other rational options available.

Epidemiology

To perform a satisfactory epidemiological study you need to know where you started from, i.e. the baseline condition. This allows for comparison with the exposed group. You also need to know about exposure – who is exposed to what – then you can measure exposure against outcome. As Dr Dorey's report makes clear, there is precious little exposure data for most of the groups of chemicals of concern. Furthermore, there are no unexposed groups to act as 'controls'. Under such circumstances, epidemiology can only be regarded as an extremely blunt tool.

The frequency of a condition in the population is also a factor to be considered. If thalidomide had not caused phocomelia (limb shortening, a relatively obvious and rare condition), but had instead caused cleft palate (a relatively common condition), the likelihood is that we still would not know of the side effects of this drug. If the chemical pollutant mixture to which we are now exposed is causing changes in the frequency of relatively common conditions such as allergy and cancer, then epidemiology is likely to be of little help, given the data gaps outlined above. Once again, we are faced with the single option of hazard reduction as a means of regulation.

Conclusions

This report strengthens the evidence base relating human exposure to environmental chemical pollutants, particularly to those members of the population most at risk, namely children. We have no toxicological tools with which to analyse the level of complexity of the mixture to which we are exposed. We have no realistic prospect of being able to use epidemiology to help analyse the effects of multiple components of the mixture. However, we do know that many of the chemicals in this mixture are indeed toxic.

In reality, the only effective remedy available to us is to reduce the exposure of the general population, on a precautionary basis, by removing from production those groups of chemicals which have been shown to potentially pose a hazard.

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Executive Summary

In early 2003, Greenpeace exposed the presence of persistent, bioaccumulative chemical pollutants in samples of house dust taken from homes across the UK. Research published by Greenpeace in October 2003 reveals that these same chemicals can be found in many consumer products readily available on every high street.

This report completes the loop of chemical exposure by illustrating two disturbing developments. Firstly, that many of the same chemicals used routinely in consumer products and present in house dust, are also present in the human body, including in prenatal and newborn children. Secondly, that these chemicals are likely to be having a detrimental effect on the health of children and the human population at large. Significantly, the report also draws together the available evidence that illustrates how and why prenatal and newly born children are particularly at risk from chemical pollutants.

The evidence presented here, from academics, governments and well-respected international institutions such as the World Health Organisation (WHO), is not easily dismissed, contributing as it does to a growing bank of international research that reinforces the conclusion of this report – that current chemical legislation is failing to protect children from a harmful chemical assault that begins from a child's conception.

The study focuses on seven key chemicals: alkylphenols (nonyl and octylphenol), bisphenol A, brominated flame retardants, organotins, phthalates, chlorinated paraffins and artificial musks. The report uses available research to demonstrate:

- the presence of these substances in children (and the human population at large)
- the ways in which children are particularly exposed to these substances
- how this increased exposure increases the potential for detrimental health impacts
- the different illnesses and diseases that are now being linked to this chemical exposure
- the specific health impacts of the key chemicals listed above.

Studies have shown that alkylphenols, found in a range of products such as leather and textile finishers and in some detergents, contaminate children before and after birth. Nonylphenol has been detected in umbilical cords, confirming that this hormone-disrupting substance is able to cross the placenta. Preliminary studies show that nonylphenol may disrupt the human immune system by adversely effecting groups of white blood cells.

Likewise, bisphenol A, which is used commonly in electrical products and as laminate coatings for the inside of food tins and bottle tops has been shown to cross the placenta and has been identified in a wide variety of human blood and tissue samples, including foetal tissue. Numerous studies have demonstrated the ability of bisphenol A to alter male reproductive organs and affect behaviour in animals at doses only a little above the amount that human infants have been shown to ingest the chemical.

One group of brominated flame retardants (BFRs) has now been banned in Europe, but others are still in use and many older

products contain the restricted substances. BFRs have been found in human blood, liver and adipose tissue, and in breast milk. Studies have shown that where BFRs are found at high levels in foetal blood, levels tend to be high in the mother's milk and blood. This indicates that maternal levels of BFRs are useful in predicting potential foetal exposure. Some BFRs have been proven to disrupt the genetic processes in cells, which in turn is known to provoke a number of diseases, including cancer.

Research has led to similar findings for organotin compounds, chlorinated paraffins and artificial musk compounds. That research is also described in this report.

Research is now beginning to illustrate that the exposure of prenatal and newborn children to these chemicals is likely to be more significant than the exposure of adults in the same environment. Recent studies have uncovered differences between children and adults in their patterns of absorption, metabolism and excretion of environmental chemicals. Children may absorb chemicals more efficiently, process them more slowly and eliminate them less efficiently than adults.

The final part of this report focuses on the kinds of non-infectious disease, such as cancer, allergies, nervous system disorders, and developmental and reproductive disorders, that are on the rise around the world. A growing body of evidence is pointing to environmental factors as contributors to these problems. Many of the chemicals that have been found in the human body have been shown to be harmful to human and animal health, and we now know that it is children that are particularly at risk. Many of these illnesses can stem from childhood, and many are suspected of being caused by damage to the developing child. This report uses the available research to illustrate the ways in which chemicals are able to damage the immune and nervous systems, interfere with hormonal activity, promote cancer and lead to other detrimental health effects.

1 INTRODUCTION

Every year around 100,000 different types of chemicals are produced for a wide range of uses around the world (EEA, 1999). Many of these chemicals find their way into our environment. Other chemicals that have been banned still leak from old products and linger in the environment, and new chemicals are synthesised every year.

Recent governmental and independent reports on the effects of chemicals on the environment and human health still focus predominantly on pollutants about which we already have a significant knowledge, while largely ignoring many other chemicals about which we know little. For example, the recent US Environmental Protection Authority report (US EPA, 2003b) on environmental pollutants and their effects on children, focused on air contaminants such as ozone and sulphur dioxide; the heavy metals lead and mercury; tobacco smoke; and pesticides. This report neglected a vast range of other chemicals which are known to contaminate humans, and about which evidence of harm is building.

The Environmental Working Group (EWG), an independent group in the USA, found 167 chemicals in the blood and urine of nine adult Americans (Houlihan et al., 2003). None of these volunteers worked with chemicals as part of their jobs, and yet each of them contained an average of 91 of the 210 chemicals tested for. Another study released around the same time by the Centers for Disease Control and Prevention (CDC) reviewed 116 chemicals in the blood and urine of adults (CDC, 2003), overlapping the EWG report by 49 chemicals. Both studies tested for certain classes of chemicals such as polychorinated bisphenols (PCBs), furans, dioxins, organophosphate and organochlorine pesticides and metabolites, heavy metals, and phthalates. The EWG included a much wider range of PCBs and pesticides, and tested for and found dozens of other semi-volatile and volatile organic compounds that are found in common consumer products. The CDC included more of the heavy metals, polycyclic aromatic hydrocarbons, well known phytoestrogens, organophosphate pesticides, and other insecticides, herbicides and fungicides.

Most of these chemicals are well-known toxins and have been studied extensively. Many are already banned or have restricted use. Neither the CDC nor the EWG report looked at levels of chemicals in children. Aside from the phthalates, neither report included a range of persistent organic pollutants (POPs) found throughout a large range of everyday household products: the alkylphenols, bisphenol A, brominated flame retardants, chlorinated paraffins, organotins, phthalates, and artificial musks.

These chemicals contaminate our air, water, soil and food. They persist in the environment and accumulate in the tissues of a range of animal life from marine snails to mammals. There is considerable evidence that these chemicals are toxic. Evidence is mounting that tiny levels can effect human health, but the level of contamination in humans is largely unknown.

Limited data shows that these chemicals are found in humans. They accumulate in our

bodies, not just from our day-to-day exposure to various products containing them, but from the time we are conceived and developing in the womb. This is the time when we are most sensitive to chemicals and their toxic effects, and the time at which damage can cause life-long health problems.

There is a wide range of health problems that affect children, or have their origins in childhood, that have been increasing in the last 50 years. These include birth defects, cancer, asthma, immune system disorders, developmental and reproductive disorders, and nervous system disorders. Many of the POPs that contaminate our bodies have been linked to these diseases.

The following sections review these POPs and their potential health effects. Section 2 reviews the levels of contamination in humans, focusing on contamination in children where data exists. Section 3 reviews how these chemicals find their way into the body and why children are more exposed. Section 4 reviews the health effects of this contamination, focusing on child health. Section 5 provides a summary and conclusion.

2 CHEMICAL CONTAMINANTS IN CHILDREN

Accurately estimating the numbers and levels of chemicals that humans are exposed to is almost impossible. It is too difficult to estimate contamination when it comes from so many different sources. Levels of chemicals in female blood can give us an idea of which chemicals an unborn child may be exposed to, but actual levels in the foetus can vary significantly from the mother's levels, depending on how much is absorbed by the placenta. Measures of contamination in the umbilical cord at birth or amniotic fluid, if amniocentesis is performed during pregnancy, are the best indicators of child contamination. Other than levels in blood, levels of chemicals in breast milk and infant food are a good indication of neonatal exposure.

The following section reviews a series of POPs with wide-ranging uses and explores the increasing evidence of their contamination of the child.

2.1 Alkylphenols

Alkylphenols are non-halogenated (halogens include bromine and chlorine) chemicals largely used to make surfactants (detergents), as well as emulsifiers, dispersants and/or wetting agents in industry and consumer applications. Alkylphenols are predominantly manufactured as alkylphenol ethoxylates (APEs), however alkylphenols themselves can be used as plasticisers in plastics, and their derivatives, alkylphenol phosphites, can be used as UV stabilisers in plastics. The most widely used alkylphenols are nonylphenols, followed by octylphenols.

APEs are found in industrial detergents, such as for wool washing and metal finishing; industrial processes such as emulsion polymerisation, leather and textile finishers; laboratory detergents including Triton X-100; some pesticides and other agricultural products; and the spermicidal lubricant nonoxynol-9. Outside Europe, APEs may also be used in many domestic products, such as liquid clothes detergents in the USA.

In Europe, most APEs have been replaced with safer alcohol ethoxylates. However, in Germany 1,000 tonnes/year of APEs are used in domestic cleaning products despite a voluntary ban on these applications (ENDS, 1999a).

2.1.1 Alkylphenols in the Child

There have been few studies on levels of human contamination by alkylphenols, but those that have been performed clearly show that children are contaminated before and after birth (Table 2.1).

Table 2.1
Human contamination by nonylphenol.

Source	Levels	Study
Umbilical cord	2 ng/kg wet tissue	Takada et al., 1999
Breast milk	0.3 mg/kg lipid	Guenther et al., 2002

Nonylphenol has been detected in human umbilical cords (Takada et al., 1999), confirming that it crosses the placenta from the contaminated mother to the growing foetus. The authors stressed the importance of further studies using larger numbers of umbilical cords, and analyses of maternal and cord blood to estimate the fraction of contaminants passing from the blood to the foetus. Nonylphenol also contaminates breast milk (Guenther et al., 2002).

2.2 Bisphenol A

Bisphenol A is a key building block of polycarbonate plastic and epoxy resins. Polycarbonate plastic is lightweight, tough, and clear with high heat and electrical resistance, and is therefore used in a wide variety

of products including digital media (e.g. CDs, DVDs), electrical and electronic equipment, automobiles, sports safety equipment, reusable food and drink containers, medical equipment, and many other products. Bisphenol A is also used as an additive in other plastics. Epoxy resins are used in electrical laminates for printed circuit boards, composites, paints and adhesives, and a variety of protective coatings. Cured epoxy resins are used as protective liners in metal cans to maintain the quality of canned foods and beverages, in bottle tops, and in water supply pipes. Some polymers used in dental treatment also contain bisphenol A. In Germany alone, approximately 210,000 tonnes of bisphenol A are produced per year (Leisewitz & Swartz, 1998).

2.2.1 Bisphenol A in the Child

The subject of the effects of bisphenol A on humans has been contentious. It has been suggested that it is only partially absorbed, has a high conversion rate to the biologically inactive bisphenol A monoglucuronide, is rapidly excreted, and shows no evidence of bioaccumulation in tissues (Schonfelder et al., 2002b). For these reasons, until recently, many scientists believed that the active parent form of bisphenol A would not be found in human plasma, and therefore no significant levels could reach the foetus.

However, studies from Germany and Japan have now confirmed that children are exposed to bisphenol A before birth. The first, a Japanese study, found bisphenol A in umbilical cords (Takada et al., 1999). Studies on mice and monkeys then showed that this chemical can cross the placenta (Uchida et al., 2002). At least six studies have since demonstrated bisphenol A in a wide variety of blood and tissues from healthy adults, and maternal and foetal tissues (Table 2.2).

Data from Ikezuki et al. (2002) suggest that bisphenol A may concentrate in amniotic fluid as it was found at approximately 5-fold higher concentrations at 15–18 weeks gestation, compared with other fluids. Schonfelder

Table 2.2
Human contamination by bisphenol A.

Source	Levels	Study
Umbilical cords	1.6 ng/g wet tissue	Takada et al., 1999
Healthy human blood	0.32 ng/mL	Inoue et al., 2000
Normal adult male blood	1.49 +/-0.11 ng/mL (mean)	Takeuchi & Tsutsumi, 2002
Normal adult female blood	0.64 +/-0.10 ng/mL (mean)	Takeuchi & Tsutsumi, 2002
Blood from women with polycystic ovary syndrome	1.04 +/-0.10 ng/mL (mean)	Takeuchi & Tsutsumi, 2002
Ovarian follicular fluids obtained during in vitro fertilisation procedures	1–2 ng/mL (mean)	Ikezuki et al., 2002
Blood from perimenopausal and pregnant women	1–2 ng/mL (mean)	Ikezuki et al., 2002
Amnoitic fluid at 15–18 weeks	8.3 +/-8.7 ng/mL (mean)	Ikezuki et al., 2002
Maternal blood at 32–41 weeks gestation	3.1 ng/mL (median) 0.3–18.9 ng/mL	Schonfelder et al., 2002b
Umbilical cord blood	2.9 ng/mL (median) 0.2–9.2 ng/mL	Schonfelder et al., 2002b
Placental tissue	12.7 ng/g (median) 1.0–104.9 ng/g	Schonfelder et al., 2002b
Amniotic fluid, normal karyotype	0.26 ng/mL (median) 8 samples showed levels of 2.80–5.62 ng/mL	Yamada et al., 2002
Amniotic fluid, abnomal foetal karotype	0 ng/mL (median)	Yamada et al., 2002
Maternal blood, normal foetal karyotype	2.24 ng/mL (median)	Yamada et al., 2002
Maternal blood, abnormal foetal karyotype	2.97 ng/mL (median)	Yamada et al., 2002
Maternal blood	0.46 +/-0.20 ng/mL (mean)	Kuroda et al., 2003
Umbilical cord blood	0.62 +/-0.13 ng/mL (mean)	Kuroda et al., 2003
Sterile patients' blood	0.46 +/-0.20 ng/mL (mean)	Kuroda et al., 2003
Sterile patients' ascitic fluid	0.56 +/-0.19 ng/mL (mean)	Kuroda et al., 2003

et al. (2002b) also showed that in 14 of 37 cases, foetal plasma levels of bisphenol A were higher than in the corresponding mother's blood. Foetal levels of bisphenol A were also significantly higher in males, which may indicate sex differences in the metabolism of this chemical. Takeuchi and Tsutsumi (2002) confirmed this gender difference in a study on adults, and suggested that it may be due to androgen (male hormones) related metabolism of bisphenol A.

2.3 Brominated Flame Retardants

Brominated flame retardants are a diverse group of compounds used to prevent combustion and/or retard the spread of flames in a variety of plastics, textiles and other materials. They can be found in a large range of industrial and electrical appliances, vehicles, lighting and wiring, textiles including carpets and furnishings, and in packaging and insulating materials such as polystyrene. Over 70 compounds or groups have been described, but three dominate:

- polybrominated diphenyl ethers (PBDEs)
- hexabromocyclododecane (HBCD)
- brominated bisphenols (such as TBBP-A)

PBDEs and HBCD are mainly used as additives. TBBP-A is more commonly used as a reactive component, becoming more tightly bound to the polymers in which it is incorporated, but some additive uses still exist. Polybrominated biphenols (PBBs) are no longer produced in Europe but substantial quantities remain in existing and imported products and wastes.

One group of PBDEs, the penta-BDEs, are being banned across Europe, however, they may still appear in the environment following degradation. For example, UV light and sunlight can cause deca-BDE to debrominate, resulting in the formation of lower-brominated diphenyl ethers such as penta-BDEs (Darnerud et al., 2001). The World Health Organisation has recommended that PDBEs not be used where suitable replacements are available, and Swedish and Danish Governments have called for PDBEs to be phased out. PBDEs were produced at a rate of 40,000 metric tons per year world-wide in 1999 (Rahman et al., 2001).

2.3.1 Brominated Flame Retardants in the Child

The majority of the contamination data is for PBB (now largely disused), and the PBDEs. Levels of human contamination by other brominated flame retardants is largely unknown.

The similarity of PBDEs to dioxins and polychlorinated biphenyls (PCBs) has been of major concern because their toxic effects may be similar, therefore these are the most studied group of brominated flame retardants. PDBEs are found in human breast milk, blood, liver and adipose tissue (Table 2.3). Extensive breast milk studies in Sweden show an exponential increase in PBDEs in breast milk (an average increase from 0.07–4.02 ng/g lipid between 1972–1997) while other chemical contaminants such as PCBs have tended to decrease (Meironyte et al., 1999). However, a recent paper has reported a decrease of PBDEs in Swedish breast milk since 1997, possibly due to a voluntary phase out of penta-BDE (Hooper & She, 2003).

This rise in human contamination was also seen in a study on human blood samples (10 male, 10 female) taken in 1985–1999 for the German environmental specimen bank. The median PBDE concentrations in blood have increased from 3.1–4.7 ng/g lipid (Schroter-Kermani, 2001). This study also showed that males may be more at risk of contamination than females as male blood samples showed 20–75% higher levels of PBDEs than female blood, depending on the sampling year.

Babies born to mothers in the USA may be most at risk of PBDE contamination. Mazdai

Table 2.3
Human contamination by polybrominated diphenyl ethers.

PBDE	Source	Levels	Study
TBDE	Human adipose tissue – healthy subjects	5.1 ng/g (mean) 0.6–27.5 ng/g	Hardell et al.,1998
TBDE	Human adipose tissue – non-Hodgkin's lymphoma patients	13.0 ng/g (mean) 1.0–98.2 ng/g	Hardell et al.,1998
PBDEs (8 identified including BDE-47)	Breast milk	4.02 ng/g lipid (mean)	Meironyte et al., 1999
PBDEs (BDE-28, 47, 66, 85, 99, 100, 153, 154)	Human blood (10 male, 10 female)	4.7 ng/g lipid (mean)	Schroter-Kermani, 2001
PBDEs (BDE-47, 99, 153, 154, 100)	Breast adipose	86 ng/g (mean)	She et al., 2002
PBDEs	Breast milk	0.67–2.84 ng/g lipid	Ohta et al., 2002
PBDEs (BDE-28, 47, 99, 100, 153, 154, 183)	Human adipose tissue	1.29 ng/g lipid (median) 0.47–2.75 ng/g lipid	Choi et al., 2003
PBDEs	Maternal blood	24.0 pg/g fresh weight (median)	Guvenius et al., 2003
PBDEs	Umbilical cord blood	4.3 pg/g fresh weight (median)	Guvenius et al., 2003
PBDEs	Breast milk	75.0 pg/g fresh weight (median)	Guvenius et al., 2003
PBDEs (6 including BDE-47)	Maternal blood	15–580 ng/g lipid	Mazdai et al., 2003
PBDEs (6 including BDE-47)	Umbilical cord blood	14–460 ng/g lipid	Mazdai et al., 2003

PBDEs: polybrominated diphenyl ethers; TBDE: 2,2',4,4'-tetrabrominated diphenyl ether

et al., (2003) found that the concentrations of PBDEs in maternal and foetal serum samples in Indianapolis, IN, USA, were 20–106 times higher than the levels reported previously in Swedish mothers and infants (Guvenius et al., 2003) and 20 times higher than Norwegian blood samples (Thomsen et al., 2002). In San Francisco Bay, CA, USA, breast adipose tissue samples from 23 women are the highest human levels reported to date (She et al., 2002).

There is a high correlation between levels of PBDE in foetal blood and the corresponding levels in the mother's milk and blood, indicating that maternal PBDE blood levels are useful in predicting foetal exposure (Mazdai et al., 2003)

The tetrabrominated PBDE congener, BDE-47, is the most abundant PBDE congener in all human samples tested, making up 53–65% of total PBDEs detected. The other major congeners include, BDE-99, 100, 153, and 154 (Schroter-Kermani, 2001; She et al., 2002; Mazdai et al., 2003).

2.4 Organotins

Organotins are organic compounds containing at least one bond between carbon and metal tin and include:

- monodibutyltins (MBT)
- dibutyltins (DBT)
- tributyltins (TBT)
- triethyltins (TET)
- triphenyltins (TPT)
- octyltins (MOT, DOT).

Mono-substituted organotins tend to be used as stabilisers, di-substituted organotins

in PVC and as catalysts in production of polyurethane foams and silicones, and tri-substituted organotins in a wide range of agricultural and general biocides, but there is some overlap in uses between the groups. Organotins can therefore be found in: antifoulants on boats, ships, quays, buoys, crab-pots, fishing nets and cages; biocides for cooling systems, power stations, pulp and paper mills, breweries, leather processing and textile mills; slimicides on masonry; wood preservatives; anti-fungal agents in carpets and PVC flooring; glass coating applications; disinfectants; heat stabilisers in rigid (pipes, panels) and soft (wall-coverings, furnishing, toys) PVC products; paint and rubber; pesticides targeting everything from insects, to worms, to rats; and anti-bacterial shoe insoles and nappies.

TBT has been banned for use on small vessels in many countries for over 10 years due to its impact on marine molluscs, and is currently being phased out of larger vessels worldwide (Champ, 2000). PVC uses about two-thirds of the global consumption of the organotins, which can make up to 2% of the finished product. Approximately 15,000 tonnes of organotins were used in PVC in Europe in 1995 (Santillo et al., 2003).

2.4.1 Organotins in the Child

Although organotins, particularly TBT, have been found in a wide range of molluscs, fish, marine birds, marine mammals, and freshwater birds (IPCS, 1999), aside from a few reports (Table 2.4), levels of contamination in humans are largely unknown, and there are no readily available reports on child contamination.

2.5 Phthalates

Phthalates are among the most ubiquitous synthetic chemicals in the environment. They are non-halogenated ester derivatives of phthalic acid. Some phthalates are used as discrete products, such as di(ethylhexyl) phthalate (DEHP), while others are complex isomeric mixtures containing individual compounds with similar structures such as the di-iso-nonylphthalates (DINP) and di-iso-decylphthalates (DIDP).

The major use for phthalates are as plasticisers in PVC products including building/furnishing materials, floorings, furniture, food packaging, toys, clothing, car interiors, cables, and a range of medical equipment such as blood bags. They are also used in solvents, lubricating oils, fixatives, adhesives, paints, sealants, surface coatings, insecticides, detergents, printing inks, car-care products, soaps, shampoos, hand lotion, nail polish, cosmetics, and perfumes. Six phthalates have been banned from use in toys designed to be put into the mouths of children under 3-years old.

Over 1 million tonnes of phthalates are produced each year in Europe alone, primarily for use in the EU (Santillo et al., 2003). The main phthalates are DEHP, DINP, DIDP, dimethylphthalate (DMP), diethylphthalate (DEP), and dibutylphthalate (DBP). DEHP constitutes about 50% of the market for PVC plasticisers in Western Europe (EC, 2003).

2.5.1 Phthalates in the Child

Metabolites of phthalates in the urine indicate a wide exposure of humans to phthalates (Barr et al., 2003; CDC, 2003; Koch et al., 2003). Phthalates have also been detected in adult blood (see Table 2.5), but child studies are scarce.

A study on premature breast development (thelarche) in female children aged 6 months to 8 years, found phthalate esters in 68% of serum samples from the thelarche patients (Table 2.6). The phthalate esters with the most common commercial uses, DEHP and DBP, were detected in the highest concentrations. For those samples with high concentrations of DEHP, one of the major DEHP metabolites, mono(2-ethylhexyl)phthalate (MEHP), was also detected. DEHP was detected in only 14% of the control samples in lower

Table 2.4
Human contamination by organotins.

Organotin	Source	Levels	Study
BTs	Human male livers	59–96 ng/g (79% TBT)	Takahashi et al., 1999
TPT	Human blood	0.17–0.67 mg/L	Lo et al., 2003

BTs: butyltins; TBT: tributyltin; TPT: triphenyltin.

Table 2.5
Human contamination of blood from adults by the phthalate DEHP.

Group	Range	Median	Positive Samples (%)	Study
Endometriosis patients (n=55)	0–3.24 µg/mL	0.57 µg/mL	92.6	Corbellis et al., 2003
Normal females (n=24)	0–1.03 µg/mL	0.18 µg/mL	-	Corbellis et al., 2003
Normal adults (6 female, 3 male)	97.2–904.8 µg/g lipid	-	100*	Houlihan et al., 2003

DEHP: di(ethylhexyl)phthalate.
*6 phthalates were detected in all 9 subjects but only DEHP was quantified.

Table 2.6
Contamination of blood from normal girls and girls with premature breast development (thelarche) by phthalates.

Phthalate	Group	Positive Samples	Range of positives (mg/mL)	Group Mean (mg/mL)
BBP	Thelarche	2/41	0.054–0.117	0.004
BBP	Normal	0/35	0	0
DBP	Thelarche	13/41	0.015–0.276	0.042
DBP	Normal	0/35	0	0
DEP	Thelarche	3/8	0.0019–0.0089	0.0055
DEP	Normal	nd	nd	nd
DEHP	Thelarche	25/41	0.187–2.098	0.450
DEHP	Normal	5/35	0.276–0.719	0.070
DEP	Thelarche	5/41	0.008–0.037	0.003
DEP	Normal	0/35	0	0
DMP	Thelarche	2/8	0.0183–0.0214	0.01985
DMP	Normal	nd	nd	nd
DOP	Thelarche	1/41	0.438	0.011
DOP	Normal	1/35	0.562	0.016
MEHP	Thelarche	5/41	0.0063–0.038	0.003
MEHP	Normal	0/35	0	0

BBP: benzylbutylphthalate; DBP: dibutylphthalate; DEHP: di(ethylhexyl)phthalate; DEP: diethylphthalate; DMP: dimethylphthalate; DOP: dioctylphthalate; MEHP: mono(ethylhexyl)phthalate. (Data from Colon et al., 2000).

concentrations. A more sensitive analysis of eight thelarche samples allowed detection of a further two phthalates, DMP and DEP, in two and three samples, respectively.

While there are few studies on the contamination of young children, other studies suggest that their levels could be at least as high as adult levels. A large study of urine phthalate levels in 2,541 USA residents showed that females tended to have higher concentrations than males (CDC, 2003). Animal studies show that phthalates cross the placenta and pass into breast milk (Dostal et al., 1987; Parmar et al., 1985; Srivasta et al., 1989), therefore, phthalates will be passed onto developing foetuses and newborn children via their mothers. Additionally, children seem to be more exposed to phthalates than adults. In the CDC study, of the seven urine phthalate metabolites tested, the highest levels of metabolites for DEHP, DBP and monobenzylphthalates were found in the youngest age-group tested: the 6–11-year-old children (CDC, 2003).

2.6 Artificial Musks

Nitro musks and polycyclic musks are a series of structurally similar aromatic compounds used as substitutes for natural musks. Artificial musks are cheap, easy to

Table 2.7
Human contamination by artifical musks.

Musk	Sample	Levels	Positive Samples	Study
Xylene	Breast milk (n=391)	100 µg/kg fat (mean) 10–1220 mg/kg	-	Liebl & Ehrenstorfer, 1993
Ketone	Breast milk (n=391)	40 µg/kg fat (mean)	-	Liebl & Ehrenstorfer, 1993
Galaxolide	Adult adipose (n=14)	16–189 mg/kg fat	-	Rimkus & Wolf, 1996
Tonalide	Breast milk (n=5)	8–58 µg/kg fat	-	Rimkus & Wolf, 1996
Xylene	Adult blood in 1993 (n=72)	0.24 ~µg/L (median) <0.10–1.12 mg/L	66/72	Angerer & Kafferlein, 1997
Xylene	Adult blood in 1998 (n=41)	<0.1 µg/L (median) <0.1–0.29 mg/L	5/41	Kafferlein & Angerer, 2001
Xylene	Blood from women with endocrine and gynaecological problems (n=154)	65.5 ng/L (median) (1183 ng/L maximum)	95%	Eisenhardt et al., 2001
Ketone	Blood from women with endocrine and gynaecological problems (n=154)	55.5 ng/L (median) 518 ng/L (maximum)	85%	Eisenhardt et al., 2001
Mosken	Breast milk (n=53)	64 µg/kg fat (mean)	4/53	Zehringer & Herrmann, 2001
Tibeten	Breast milk (n=53)	25 µg/kg fat	1/53	Zehringer & Herrmann, 2001
Xylene	Breast milk (n=53)	35 µg/kg fat	1/53	Zehringer & Herrmann, 2001
HHCB	Breast milk (n=53)	73 µg/kg fat (mean)	52/53	Zehringer & Herrmann, 2001
AHTN	Breast milk (n=53)	44 µg/kg fat (mean)	37/53	Zehringer & Herrmann, 2001
Traseolide	Breast milk (n=53)	74 µg/kg fat	1/53	Zehringer & Herrmann, 2001

produce fragrances that are added to personal care and household products such as laundry detergents, shower gels, soaps, hand lotions and perfumes. Some musks are also used as additives in food, room fragrances, chewing tobacco, fish baits, Indian joss sticks, and in technical products such as herbicide formulations and explosives. The nitro musks include musk xylene, musk ketone, musk ambrette, musk tibetene and musk moskene. The major polycyclic musks are tonalide and galaxolide, also know as AHTN and HHCB respectively.

Musk ambrette has been banned and musk xylene restricted due to health concerns. They are largely being replaced with polycyclic musks which may appear less problematic but are, in fact, largely untested.

2.6.1 Artificial Musks in the Child

Nitro musks have been found in human adipose, breast tissue and blood (Table 2.7) but no studies appear to have been done on children. However, adult female blood and breast milk levels indicate that contamination of the foetus and newborn does occur.

2.7 Chlorinated Paraffins

Polychlorinated-n-alkanes or chlorinated paraffins (CPs) are produced by reacting chlorine gas with paraffins (hydrocarbons) (Fig. 2.6). They are complex mixtures and exist as oils or solids depending on their content of chlorine and carbon. They are divided in to six groups depending on carbon chain length (short C10–13; intermediate C14–17; long C18–30) and degree of chlorination (low <50%; high >50%).

They are used as high-temperature lubricants, plasticisers, flame retardants, industrial cutting oils for metal working, finishing agents for leather goods and textiles, and additives in adhesives, paints, rubber and sealants. Some short chain CPs are being used as replacements for PCBs. They are also used as secondary plasticisers for PVC or as partial replacements for primary plasticisers such as phthalates. In 1998, about 4000 tonnes of CPs were produced in the EU (Santillo et al., 2003).

2.7.1 Chlorinated Paraffins in the Child

Data on the human contamination by CPs is scarce. One report from 1985 on the contamination of environmental samples by CPs includes a sample of human fat (200 µg/kg fat) (Schmid & Muller, 1985).

3 CHILD EXPOSURE TO CHEMICALS

The suite of chemicals to which children are exposed is not measured or defined by any programme. Testing, labelling and monitoring programmes capture only a fraction of the chemicals we are exposed to. Children are exposed to so many different sources of chemicals that it is very difficult to estimate which chemicals are important and at what levels. In addition, due to the combined effects of development, physiology, diet and behaviour specific to their age group, children may experience higher levels of exposure to toxins than adults within the same environment.

An increasing number of studies have uncovered differences between children and adults in their patterns of absorption, metabolism and excretion of environmental chemicals. Children may absorb chemicals more efficiently, process them more slowly and eliminate them less efficiently than adults. Children may be more or less sensitive to the particular effects of a chemical, and the chemical may produce different adverse effects. It is clear that studies of adults must be used cautiously to predict potential adverse effects in children.

This section looks at the ways in which children are contaminated by chemicals, and explores why they are more susceptible to this contamination.

3.1 From Products to Children

About 100,000 different chemicals are registered for commercial use within Europe with hundreds of new chemicals registered each year (Goldman, 2002). In 2001, major USA industries reported the release of 6.16 billion pounds of industrial chemicals into air, water and landfill (US EPA, 2003b), just a portion of what is actually released. Chemicals can also leach from their products, contaminating food, homes and work places.

The majority of the chemicals described in Section 2 are persistent; that is, they stay in the environment for a long time. Those chemicals that are described as having a relatively short half-life are regularly released into the environment in such large amounts that they are constantly detectable. For example, despite having a relatively short half-life in the body (about 12 hours), phthalate metabolites in the urine of women in one study remained fairly constant from day to day, suggesting a constant daily exposure (Hoppin et al., 2002).

Many of these chemicals are also bioaccumulative; that is, they accumulate in the bodies of organisms, some in the fat tissue and others in specific sites such as liver and kidney. These chemicals then build up in the food chain so that those organisms at the top of food chains, such as humans, have the highest exposure. The developing child, who feeds directly from the mother's body or breast milk, sits at the top of many food chains.

3.1.1 Prenatal Exposure

By the third month of pregnancy, the placenta has sent extensive branches into the deep layers of the uterus (Moore & Persaud, 2003). These are intertwined with the spiral arteries of the uterus which send jets of blood between these branches. As the mother's blood trickles between the placental branches, carbon dioxide and metabolic wastes are taken away and replaced with oxygen, water, minerals, nutrients and antibodies. This is a similar process by which the blood in our capillaries are cleaned and refuelled, with one major difference – the placenta actively pumps most of what it needs (with the exception of oxygen) from the mother rather than relying on passive diffusion. Therefore, the foetus is guaranteed a constant supply of required substances, even if the mother's blood levels are unusually low or high in a particular component. In this way, the placental barrier can decide, to some extent, what enters the developing child.

When it comes to toxic chemicals that have contaminated the mother, however, the placenta is not really a barrier. Chemical substances from the mother's blood are sorted primarily on the basis of molecular weight, electrical charge and lipid solubility. Small, neutrally charged molecules that readily dissolve in fat are given free passage through the placenta, regardless of their potential for harm. Methylmercury, for example, is actively pumped from the mother's blood so that the mercury levels in the umbilical cord will eventually surpass the levels in the mother's blood.

The foetus, suspended by the umbilical cord, floats freely in amniotic fluid which surrounds, protects, and bathes the developing foetus (Moore & Persaud, 2003). This fluid, made by tissues from both the foetus and mother, is constantly sipped and swallowed by the foetus, and is absorbed by the digestive tract. It soaks through the skin, and is inhaled as the baby practices breathing. It is absorbed by the foetus, enters the foetal circulation, and leaves via the maternal circulation. It bathes the inside and outside of the developing baby, as do any chemicals which contaminate it.

As well as being exposed to the chemicals which the mother is exposed to daily, the developing foetus is exposed to chemicals that have been stored in her tissues, and are released during pregnancy. For example, there is a dramatic mobilisation of maternal fat stores during the third trimester, a period critical to brain development (Moore & Persaud, 2003).

Bisphenol A is a good example of the problem. In many cases, foetal plasma levels of bisphenol A are higher than for maternal blood (Schonfelder et al., 2002b). Bisphenol A concentrations in amniotic fluid at 15–18 weeks gestation were five times higher than in other fluid in one study (Ikezuki et al., 2002). The rate of clearance of bisphenol A from the blood is slower in foetuses because the enzymes required to clear it are not expressed until after birth. Women also have higher concentrations in their blood than men, due to differences in either exposure or metabolism between the sexes (Schonfelder et al., 2002).

3.1.2 Postnatal Exposure

Food

The major source of exposure to bioaccumulative chemicals is food (for example, see Table 3.1). Food is first contaminated via environmental pollution during growth and bioaccumulation along the food chain. This contamination continues due to leaching from components and packaging used during manufacturing, processing and storage, particularly for food containing higher levels of fat.

Fish tends to be the most highly contaminated of all food. For example, the flame retardant PBDEs have been detected in fish and

Table 3.1
A comparison of the estimated daily intake of the phthalate, DEHP, from varying sources by different age groups in Canada (µg/kg body weight per day).

Age (years)					
Source	**0.0–0.5**	**0.5–4**	**5–11**	**12–19**	**20–70**
Food	7.9	18	13	7.2	4.9
Indoor air	0.86	0.99	1.2	0.95	0.85
Drinking water	0.13–0.38	0.06–0.18	0.03–0.10	0.02–0.07	0.02–0.06
Soil	0.000064	0.000042	0.000014	0.000004	0.000003
Ambient air (Great Lakes)	0.00003–0.0003	0.00003–0.0003	0.00004–0.0004	0.00003–0.0003	0.00003–0.0003
Total	8.9–9.1	19	14	8.2	5.8

(Data from Meek & Chan, 1994).

shellfish in the range of 21–1650 pg/g fresh weight (Ohta et al., 2002). In comparison, beef, pork, and chicken contained 6.25–63.6 pg/g, and three different vegetables had levels of 38.4–134 pg/g. Similarly, in Japan where fish is a major part of the diet, the estimated daily intake of the organotin TBT is relatively high (2.5 µg/kg body weight based on a fish consumption of 150 g/day) (van Heijst, 1994). Ohta et al. (2002) also showed a strong correlation between PBDE levels in breast milk and intake of fish and shellfish.

Preparation and storage of food can increase contamination dramatically. Bisphenol A, which leaches from unreacted materials and/or degraded polymers from plastics, is a good example. Bisphenol A levels migrating from plastic products into baby food increase after dishwashing, boiling, and brushing (Brede, 2003); it migrates from rubber products and plastic stretch-film used in food-contact (Lopez-Cervantes & Paseiro-Losada, 2003; Ozaki & Baba, 2003); and an estimated 80–85% of food cans contain bisphenol A.

In the case of the organotins, TBT, DBT, and MBT can leach from baking parchment, while DBT and MBT leach from gloves for kitchen work, dish-washing sponges, and cellophane film for food (Takahashi et al., 1999). Similarly, in another study, the process of frying and packaging chicken increased the phthalate DEHP content from 0.08–16.9 mg/kg. The main source of contamination was PVC gloves used by food workers (Tsumura et al., 2001b). PVC tubing has also been a source of high-level contamination of baby food (Tsumura et al., 2001a)

As an example of the extent of chemical contamination of food, a recent report found nonylphenol in all 60 food-products tested (Guenther et al., 2002). These were all popular, common foods in Germany and included 39 adult foods, from marmalade to sausages, 20 baby foods, and one sample of breast milk (see Table 3.2 for a selection of the results). Nonylphenol was detected in every sample within the range of 0.1–19.4 µg/kg, and was not related to fat content. The authors pointed out that the foods varied substantially in preparation methods and packaging and that there are multiple entry points for nonylphenol into the food supply.

Table 3.2
Examples of nonylphenol levels in infant foods, and general foods that may be fed to infants.

Food	Nonylphenol Levels (µg/kg)
Breast milk (35-year old mother)	0.3
Infant formula 1	1.6
Infant formula 2	2.1
Banana & milk puree	0.2
Peach & honey puree	0.4
Carrots puree	0.8
Semolina & vanilla puree	1.8
Broccoli, potato, turkey puree	1.4
Beef, potato & rice puree	3.1
Noodles in ham & tomato sauce	4.0
Peach & passion fruit yoghurt	0.6
Whole milk (3.5%)	0.4
Evaporated milk (10%)	3.8
Hen's egg	1.5
Tuna	8.1
Apples	19.4
Orange juice	0.1

(Data from Guenther et al., 2002).

Air

The second highest source of chemical contamination is air (Table 3.1). Indoor exposures to chemicals, including alkylphenols, bisphenol A and phthalates, in preschool children have been shown to be greater indoors than out (Wilson et al., 2003). Chemicals build up from cleaning compounds, personal care products and cosmetics. Vapours and degraded materials leach from carpeting, paints, computers, furniture and toys, and adhere to aerosol particles.

For example, DINP and DEHP are the predominant phthalates that migrate from children's toys and childcare articles (Bouma & Schakel, 2002). Various studies have found a wide range of chemicals in the dust of many houses, including alkylphenols, bisphenol A, organotins, flame retardants, phthalates, and chlorinate paraffins (Santillo et al., 2003).

Outside air contains lower levels of these chemicals, some of which may come from vaporisation from contaminated water and may show seasonal trends (Ying et al., 2002). For example, air in urban New York and New Jersey in the USA, contained nonylphenol at levels of 2.0–70 ng/m^3 due to vaporisation from the Hudson River (Dachs et al., 1999).

Water

Water is contaminated with chemicals via sewage, industry waste-water, and leaching from land-fill. APEs in treated waste-water effluents, for example, are similar in Spain, the UK and the USA with concentrations up to 369 mg/L while in sediment they reach up to 13,700 mg/kg in the USA (Ying et al. 2002).

Research by the UK Government's Drinking Water Inspectorate has shown that various products for drinking water pipes (plastic resins, rubbers, cements and pipe-linings) leach alkylphenols and phthalates into the drinking water (ENDS, 1999b). One epoxy resin coating leached two phthalates, DBP and DBEP, at levels of 1,400 µg/m^2 and 280 µg/m^2 respectively, and the alkylphenol, nonylphenol, at levels of 160 µg/m^2 into water for the first hour after curing. A solvent-based cement coating leached 12,000 µg/m^2/h of nonylphenol polyethoxylate immediately after curing, and leaching rates remained high after three days.

Contamination can even come from water filters. For example, following purification of tap water for laboratory use, bisphenol A levels increased from 0.01–0.02 ng/mL (Inoue et al., 2000).

Medical Sources

Many medical devices contain plastics, including blood bags, mechanical ventilators, haemodialysis machines, feeding equipment, and infusion lines. Therefore, medical interventions can increase exposure to chemicals used in plastics. Neonates, particularly premature neonates receiving multiple interventions in intensive care units, are exposed to high levels of plastic additives. A particular problem is DEHP, the only phthalate currently used in medical devices, which contain on average 20–40% DEHP by weight (EC, 2002). Bisphenol A can also be a problem as, for example, haemodialysis patients have additional exposure to the chemical through polycarbonate components in dialysis machines (Yamasaki et al., 2001).

3.2 Increased Exposure in Children

3.2.1 Diet

Young children eat 3–4 times more food in proportion to their body size than adults (Table 3.3), and therefore ingest more chemicals per unit of body mass. They also eat a more limited range of food – human milk or cow milk-based products are the predominant source of energy and nutrients in the first year of life. Children are therefore exposed to a higher proportion of lipid-soluble chemicals that are released into milk from the fat stores of both human mothers and cows.

Children also drink more water relative to their body mass. Infants below 6 months old consume 88 mL/kg/day of tap water, directly and via sources such as fruit juice and formula, and infants aged 6–12 months ingest 56 mL/kg/day. In contrast, adults over 20 years ingest only 15 mL/kg/day (Altshuler et al., 2003c).

3.2.2 Behaviour

Ingestion of toxins from non-dietary sources is relatively high in young children because they constantly place objects and fingers in their

mouths, particularly those going through the period characterised by intense oral exploratory behaviour. Soil may be ingested inadvertently or by deliberate or compulsive behaviour, and this may be greater in retarded children (Altshuler et al., 2003). Children also tend to paddle or swim more often, and are thus exposed to more water-borne chemicals.

Table 3.3
Energy intake of children at selected ages (kcal/kg/day).

Age	Males	Females
0–1 month	116	116
2–3 months	100	100
6–9 months	85	85
2–3 years	81	81
4–6 years	72	64
12–13 years	59	52
18–19 years	48	41

(Data from Bearer, 1995)

3.2.3 Stature

During infancy and toddler years, children spend a large amount of time on or near the floor or ground. Here they are more exposed to dense vapours, car exhausts, house dust and chemicals leaching from floor coverings.

3.2.4 Enhanced Absorption

Dermal Absorption

Children have a higher skin surface area to body weight ratio than adults, and experience more intensive contact with home surroundings, so increased dermal absorption of chemicals may occur. The skin of children is also more permeable than adult skin. In newborns, keratinisation (thickening and toughening of the skin) does not occur until 3–5 days after birth, and is more delayed in premature infants (Bearer, 1995). Studies have shown enhanced absorption of toxins including various dyes, drugs and disinfectants through the skin of newborns (Eichenfield & Hardaway, 1999).

Gastrointestinal Absorption

Gastrointestinal (GI) absorption is increased in children under 6–8months old, and the immature GI tract shows prolonged gastric emptying time and a prolonged intestinal tract transit time. This means that children will be more exposed to ingested chemicals. For example, children absorb 50% of ingested lead compared to 10% by adults. Newborns do not achieve adult levels of stomach acidity until several months of age which may increase or decrease the absorption of different chemicals (Bearer, 1995).

Respiratory Absorption

Young children breathe about twice as much air in proportion to their body mass as adults and therefore inhale proportionately more airborne chemicals (Altshuler et al., 2003c).

Brain Absorption

The blood–brain barrier (BBB) limits the ability of most chemicals to penetrate the brain from the general circulation. Lipid-soluble compounds can cross more easily as the lipid content of the brain is high. However, the effectiveness of the BBB is age-dependant – the BBB develops gradually during foetal growth and infancy, and matures during childhood (Altshuler et al., 2003c). This higher permeability to chemicals may result in higher exposures of the brain to toxins.

3.2.5 Distribution in the Body

Blood and body composition and organ size in infants and children differ from adults. This affects the distribution and storage of chemicals, and thus the exposure of organs and tissues to their toxic effects. In the blood, for example, chemicals may be bound to special blood proteins that prevent them from accessing target sites in organs. Bound chemicals are less likely to cause adverse effects in the body. However, serum albumin, the predominant binding protein in blood, only reaches adult levels by the age of 10–12 months (Altshuler et al., 2003c). Thus, infants are more vulnerable to toxins as they lack this protection. Infants also have a higher percent-

age of water and a greater volume of extracellular fluid than adults – 75% of body weight at birth compared to 50–60% in an adult – and therefore can carry proportionately more chemicals in their body fluids.

In older children and adults, fat can act as a buffer to lipid-soluble toxins, by storing them and releasing them slowly over a period of time. The developing foetus lacks this buffer as it has little body fat until the last four weeks of gestation (Moore & Persaud, 2003). Fat-soluble chemicals are, therefore, more likely to be stored in foetal tissues with a higher fat content, such as the highly sensitive, developing brain.

Some organs in the child are larger than those of an adult in relation to their body mass, and blood flow to their organs may also be greater in proportion to body mass. For example, the infant brain makes up 13% of total body mass, while an adult brain is only 2%, and cerebral flow is greater per unit mass of brain weight than for an adult (Altshuler et al., 2003c).

All these factors may result in a greater distribution and storage of certain chemicals in the organs of children. An increase in storage can then extend the duration of exposure to chemicals, as they are slowly re-released over time.

3.2.6 Metabolism

Children have a large skin surface in proportion to their body mass and therefore lose body heat more rapidly. This requires a higher resting metabolic rate than adults and more oxygen relative to their body mass. They also tend to be more active than adults, further increasing their respiration rate and energy metabolism. Therefore, both their food and air intake is higher and their exposure to polluting chemicals is greater per unit of body mass than for adults.

3.2.7 Biotransformation of Chemicals

Biotransformation of a chemical into its metabolite(s) may either increase or decrease its toxicity, and make it easier or harder to eliminate it from the body. In infants and children, many important biotransformation pathways do not function at adult levels, and some transformation processes follow different pathways (Bearer, 1995; McCarthy, 2003). These differences can result in an inability to metabolise a chemical, or the production of different metabolites in the developing foetus or child compared to adults. Immaturity can be an advantage for those chemicals where the metabolite is more toxic than the parent chemical; however, in general, reduced metabolic capacity of infants and children probably predisposes them to the risk of more severe adverse effects than adults.

3.2.8 Excretion and Elimination

Chemicals may be excreted as the parent compound, metabolite, or linked to other chemicals (conjugates) via urine, faeces or expelled air. Some chemicals are transformed to water-soluble products so that they can be excreted by the kidneys via glomerular filtration, tubular diffusion, or tubular secretion. Glomerular filtration removes most toxins unless they are tightly bound to plasma proteins.

The liver and kidneys of newborns are not fully developed at birth and so toxins are eliminated more slowly than they are in adults (McCarthy, 2003). The glomerular filtration rate of a full-term newborn is about 50% that of an adult and reaches the full capacity at about 12 months. Tubular secretion and renal blood flow reach adult rates by about 6–9 months and 5–12 months, respectively (McCarthy, 2003).

Due to a combination of differences in biotransformation and immature organ function, it can take neonates 2–9 times longer on average to eliminate a chemical from their body, depending on the primary elimination pathway for the chemical (Ginsberg et al., 2002). In 7% of newborns, this can be over 10 times longer (Hattis et al., 2003).

4 CONTAMINATING CHEMICALS AND DISEASE

A range of non-infectious diseases around the world are on the rise. Environmental factors are believed to contribute to all these diseases, although specific factors or chemicals may not have been identified. All these diseases can stem from childhood, and many are suspected to be caused by damage to the developing child, the period of life most susceptible to chemical damage.

Many of the hundreds of chemicals which have been shown to contaminate our bodies are toxic to a range of animals. The effects of these chemicals on human health are largely unexplored, partly because they are found in doses in the environment that were once considered unlikely to have an effect. Research is now linking low-dose chemical studies in animals to a broad range of health effects that were previously unexplored in high-dose studies. These health effects are all related to diseases seen in humans.

This section reviews the diseases that are on the rise, and describes the periods of child development that are vulnerable to chemical damage. The final part presents the current evidence of the toxic effects of low doses of persistent organic pollutants and their possible links to disease.

4.1 Diseases on the Rise

4.1.1 Infant Mortality

The USA still has one of the highest infant mortality rates and the highest rates of preterm and low birth-weight babies in the industrialised world (Altshuler et al., 2003a). Table 4.1 shows the ten leading causes of death for newborns in the USA. About 55% of these infant deaths are attributed to:

- congenital abnormalities
- complications of low birth weight and prematurity
- sudden infant death syndrome
- complications of labour and delivery.

The risks of developing these disorders are all increased by exposure to chemicals. While deaths from most of these causes are declining, congenital abnormalities do not appear to be declining.

4.1.2 Immune Diseases

The incidence of asthma, allergies and autoimmune diseases are increasing world-wide:

- 100–150 million people suffer from asthma world-wide, and the annual death rate has reached over 180,000 (WHO, 2002). In Western Europe, the incidence of asthma has doubled in the last 10 years (WHO, 2002). While most asthma is due to allergy, there are many cases where an allergic cause has not been established.
- 1 in 4 people in the UK (15 million) are affected by an allergy at some time in their lives. The incidence appears to be increasing at a rate of about 5% a year with as many as half of those now affected being children (Allergy UK, 2003).
- 1 in 31 people in the USA (over 8.5 million) have autoimmune diseases, which include diabetes, rheumatoid arthritis and multiple sclerosis, with the incidence in women occurring at 2.7 times the rate in men (Jacobsen et al., 1997).

While there is no doubt that genetic predisposition is an important determinant for immune disease, environmental factors do play a role in their development. Studies show that certain chemicals cause changes in the immune system – from changing immune parameters such as antibody levels and white blood cell numbers, which affects the body's ability to fight infections and cancer, to inducing allergy and autoimmune diseases.

A life-long capacity for immune response is determined during prenatal and early postnatal development (EHP, 1996; Luster et al., 2003). Impairment of the immune system can result from alterations in the development

Table 4.1
Infant mortality rates and percent of total infant deaths for the ten leading causes of infant deaths in 1999 in the USA.

Rank	Cause of Death	Death Rate[1]	Total Deaths (%)
NA	All Causes	705.6	100
1	Congenital malformations, deformations and chromosomal abnormalities	138.2	19.6
2	Disorders relating to short gestation and low birth weight, not classified elsewhere	110.9	15.7
3	Sudden infant death syndrome	66.9	9.5
4	Newborn affected by maternal complications of pregnancy	35.3	5.0
5	Respiratory distress syndrome	28.0	4.0
6	Newborn affected by complications of placenta, cord and membranes	25.9	3.7
7	Accidents (unintentional injuries)	21.3	3.0
8	Bacterial sepsis of the newborn	17.5	2.5
9	Diseases of the circulatory system	16.8	2.4
10	Atelectasis[2]	16.3	2.3
NA	All other causes	228.3	32.4

[1]Deaths per 100,000 live births

[2]Atelectasis is a collapse of lung tissue affecting part or all of one lung. Congenital atelectasis can result from a failure of the lungs to expand at birth and may be localised or may affect all of both lungs.

(Data from Hoyert et al., 2001).

of the immune system and may be long-lasting. The effects may not be manifested at birth and may not be expressed until adulthood (EHP, 1996).

Chemicals can also worsen the symptoms of immune diseases. For example, children are particularly susceptible to developing asthmatic symptoms and other respiratory problems when exposed to air pollution (Altshuler et al., 2003a).

4.1.3 Cancers

Cancer is the cause of 26% of deaths in the UK and the second leading cause of death in the USA (Cancer Research UK, 2003b; Anderson, 2001). It is estimated that one in three people will develop cancer during their lifetimes. About 1.2 million people in the UK are currently diagnosed with cancer (Cancer Research UK, 2003a).

Cancer is the third most common cause of death among children between 1–19 years (Anderson, 2001). The incidence of childhood cancer in the USA increased by 26% between 1975–1999. The biggest rise was estimated for brain and other nervous system cancers (50% increase) and acute lymphocytic leukaemia (62% increase). Only 5–10% of cancers have been linked to genetic factors, the rest are influenced by a broad range of environmental factors.

Most childhood cancers differ from adult cancers and affect a wider range of cell types. Some are linked with specific genetic or chromosomal alterations that most likely occur at conception or shortly after (Altshuler et al., 2003a). Others appear to be related to the defective development, or dysgenesis, of organs or tissues (Sonnenschein & Soto, 1999). These tissues are considered to be in a pre-malignant state as they have a high risk of developing cancer. Some of these cancers, such as the liver tumour hepatoblastoma

appear in earlier in childhood, while others, such as testicular cancer in undescended testes, may appear later. In contrast, adult cancers mostly affect the epithelial cells which line organs and structures, and are thought to result from the slow accumulation of genetic or structural damage due to ageing or to exposure to environmental factors. Sensitivity to cancer-causing effects of chemicals is much greater during the pre- and postnatal period.

4.1.4 Nervous System Disorders

There appears to be an epidemic of developmental, learning and behavioural disabilities in children (Shettler et al., 2000). About 17% of children in the USA suffer from one of these disabilities. The number of children being treated for attention deficit disorder (ADD) and attention deficit hyperactivity disorder (ADHD) has increased dramatically in the last ten years (Houlihan et al., 2003; Shettler et al., 2000). The reported incidence of autism is also increasing (Houlihan et al., 2003). The causes are not known but chemical exposures are considered a potential contributor (Woodward, 2001).

Neurodegenerative diseases such as Parkinson's disease, may also be caused by chemicals. For example, exposure to heavy metals, pesticides, and tobacco smoke have been linked to Parkinson's disease (Siderowf & Stern, 2003; Woodward, 2001).

4.1.5 Developmental and Reproductive Disorders

Reproductive disorders, particularly in the male are increasing:

- Sperm counts in many parts of the world are decreasing by about 1% per year in industrialised countries. There are significant regional differences in sperm counts that cannot be explained by genetic factors (Swan et al., 2000).
- Incidence of hypospadias, a birth defect of the penis where opening of the urethra occurs at the bottom of the penis instead of the tip, doubled in the USA between 1970–1993 (Paulozzi et al., 1997).
- Cryptorchidism, where testicles fail to descend into the scrotum before birth, occurs in 2–5% of male babies in Western countries, and is increasing. Men born with this defect are also at a higher risk for testicular and breast cancer (Paulozzi, 1999).
- Testicular cancer is rising in some parts of the world. It is the most common cancer in men aged 20–34 years (Huyghe et al., 2003).

Testicular dysfunction, hypospadias, cryptorchidism and a higher risk of testis cancer are collectively known as 'testicular dysgenesis syndrome' and are recognised as likely to be caused by a disruption of sex hormones during development (Skakkebaek et al., 2001). The decreasing number of male births compared with females in many industrialised countries may also be linked to these defects in male reproduction (Davis et al., 1998; Grech et al., 2003).

There have also been decreases in the average age of puberty in some ethnic groups in the USA and other countries (Herman-Giddens et al., 1997; Krstevska-Konstantinova et al., 2001). An earlier age at puberty is associated with increased risk of impaired stature and early onset of risky behaviours, impairments in endocrine or reproductive function, and may be associated with an increased risk of cancer (Alshuler et al., 2003b).

A wide variety of chemicals have been identified that act as endocrine disrupters by mimicking or antagonising the effect of hormones, and/or disrupting the synthesis and metabolism of hormones and their receptors. Chemical endocrine disrupters may be playing a role in the rise of reproductive and developmental disorders.

4.2 Vulnerable Stages in Developing Cells

4.2.1 Control of Cell Division

The process that a cell goes through to reproduce its DNA and divide to produce new cells is called the cell cycle. The cell undergoes four phases: gene expression and protein synthesis (G1) prepare the cell for the reproduction of its DNA (S), and then further protein synthesis and growth of the cell (G2) occurs prior to the final mitosis or dividing of the cell (M1). This process involves the interaction of many metabolic and control pathways, any of which could be targets for toxins. There are checkpoints throughout the cell cycle to prevent the cell moving into the next stage if previous stages are not completed properly. Each of the 210 cell types in the human body has its own cell cycle length, from a few hours to several months or more. A short cycle, with more rapid metabolic activity generally makes cells more vulnerable to toxic effects.

Embryonic cells generally have very short cell cycles. For example, in early pregnancy, the brain grows at a rate of 250,000 cells per minute (Chudler, 2003). A common regulatory failure in rapidly cycling embryonic cells is for G2 checkpoints to be bypassed. If checkpoint molecules have been inhibited by a toxin, the cell cycle may continue without all the specifications being met, which can lead to cell abnormalities and/or cell death (Altshuler et al., 2003b).

4.2.2 Programmed Cell Death

Cell types and numbers in specific organs are controlled by both production and by removal through programmed cell death, or apoptosis. For example, apoptosis removes the webbing between the fingers, and removes populations of cells from the immune system that could cause autoimmune disease. Apoptosis plays a critical role in the developing nervous system, from early proliferation of brain cells and into postnatal life. Disruption of normal patterns of apoptosis through altered gene expression or failure of signalling mechanisms is implicated in a wide range of diseases including autoimmune diseases and certain cancers. For example, the persistence of renal stem cells that should disappear 4–6 weeks before birth may make them vulnerable to postnatal exposures that transform them into Wilm's tumour, a relatively common childhood cancer (Sharpe & Franco, 1995). Disordered apoptosis during embryonic development may increase the risk of neurodegenerative illnesses such as Parkinson's and Alzheimer's diseases (Brill et al., 1999).

4.2.3 Gene Expression

Gene expression, the translation of DNA into RNA and the transcription of RNA into proteins, controls cell division, apoptosis and metabolic activity of the cell. During development, gene expression is extraordinarily active. A high proportion of genes are being expressed and a large number of genes are being switched on or off to control the cell's activities. Such a high rate of activity provides a wide range of opportunities for chemicals to interfere with cell development by interacting directly with DNA to disturb gene expression, or with the expressed proteins such as enzymes or control molecules.

For instance, cell signalling within and between cells, is key to gene expression, cell migration, and other developmental mechanisms. Toxins that interfere with these vital molecular processes can cause permanent damage to a child's development. Brain development, for example, can be altered when the signal transduction of neurotransmitters is disrupted by the well-known toxins, alcohol and methylmercury (Altshuler et al., 2003b). Disruption of cell signalling processes has also been implicated in the development of cancer (Sonnenschein & Soto, 1999).

4.2.4 Cell Differentiation and Maturation

Cells differentiate and mature to assume their specific form and function within their organ or tissue. This is under the control of inter- and intra-cell signalling. If cells fail to differentiate properly, following chemical or other interference, organ function may be compromised and foetal survival endangered. These undifferentiated cells are also more vulnerable to further effects of chemicals, particularly those that cause cancer. For example, developmental disturbances during liver organogenesis in the first trimester of pregnancy can lead to the embryonal liver tumour hepatoblastoma. Extremely low birth weight infants are 100 times more likely than normal birth weight infants to develop hepatoblastoma and its development has been linked to environmental causes (Ikeda et al., 1997; Maruyama, 1999).

4.3 Vulnerable Stages in Child Development

4.3.1 Germ Cell Development

Sperm and egg cells (germ cells) begin developing in the foetus and mature during puberty. In the male the primordial germ cells develop *in utero*. From puberty they undergo constant cycles of growth, cell division, mitosis and meiosis to produce sperm. In females the germ cells undergo mitosis and the 1st phase of meiosis during foetal life. By puberty there are about 400,000 primary follicles. During each menstrual cycle, a group of follicles ripen, and one egg is released at ovulation.

Germ cells can be damaged during their development in the foetus, and during childhood or adult life. Chemicals that harm germ cells can harm an adult's fertility and can result in congenital health problems in their children. The male reproductive system is particularly sensitive to chemicals due to their rapid cell cycle.

4.3.2 Embryonic and Foetal Development

From the time the sperm and egg unite (conception) to birth, human life grows rapidly from a single cell zygote to an infant. Due to the complexity and speed of development and the high rate of growth throughout the prenatal period, this stage of development is more vulnerable to environmental exposures than any other period of development. There are three main stages of prenatal development:

- Periconceptual – (weeks 1–2 following fertilisation)
- Embryonic – weeks 3–7
- Foetal – weeks 8–38.

During the periconceptual period, the zygote undergoes rapid cell division, implants into the wall of the uterus and forms the embryo. During this period, hazardous environmental exposures usually cause death rather than injury, resulting in spontaneous abortion (Moore & Persaud, 2003).

Most major organs begin to form during the embryonic period, with their growth and development continuing during the foetal stage and in infancy for some systems. The period of organ development varies from 3–8 weeks to 12–16 weeks depending on the organ system. The critical period for the development of the brain, for example, is the longest at 3–16 weeks. Disruption of development during this time can result in major disruptions in the large-scale structure of organs of other structures. This may result in death but is more likely to form major physical malformations (congenital anomalies). Both the organ affected and the anomaly that results are highly dependent on both the chemical and the age of the embryo or foetus. For example, the drug diethylstilbestrol caused twice as many genetic abnormalities in male children if mothers took the medication before the eleventh week than after (Moore & Persaud, 2003).

During later stages of development, environmental exposures can result in impaired growth, physiological defects, or functional deficiencies. These effects may be manifest as low birth weight, prematurity, pregnancy complications, or late foetal death (Moore & Persaud, 2003).

4.3.3 Infancy and Childhood

Major structures of the brain and other systems continue to develop throughout childhood. For example, in the brain and nervous system, neurone migration, cell proliferation, and synapse formation are all very active from birth through to 3 years. The development of cellular insulation around nerve fibres continues for at least 10 years (Rice & Barone, 2000).

The immune system develops extensively during childhood as immune memory (the ability to recognise and respond to foreign proteins and organisms) is established (Luster et al., 2003). Improper development of the immune system may` cause allergies and autoimmune diseases later in life.

4.3.4 Puberty

Physical growth and maturation continue through puberty, particularly sexual maturation. This process is accompanied by complex interactions between the central nervous system and hormone-secreting organs, which can be affected by environmental factors.

4.4 Health Effects of Contaminating Chemicals

A growing body of literature is now linking low-dose chemical studies in animals to a broad range of health effects that were previously unexplored in high dose studies. These are subtle but important changes in the functions of apparently undamaged organ systems including alterations in immune function, enzyme activity, hormone levels, neurobehavioral parameters, organ growth, and neurotransmitter levels. Many low dose effects are detected following developmental exposure. Low doses can produce more serious effects during foetal development or infancy than similar exposures during adulthood. These studies are easier to relate to human health than high dose studies as they are within the dose range of normal hormone activities, and concentrations of contaminating chemicals in the body. Low dose studies also show that chemicals can produce a spectrum of health effects that vary with dose, and affect the target organ in different ways depending on the dose. For example, many hormone mimics produce opposite effects at low and high doses (known as a biphasic response).

While low-dose animal studies are difficult to relate to humans, they are likely to be the best indication of toxicity we can have. Direct evidence of the contaminating chemicals on human health is difficult to find as there are no control groups to compare to – we are all exposed to multiple chemicals and at widely varying levels. A second problem is that there is little data on the combined effects of chemicals – each chemical tends to be tested individually. A full understanding of their effects on humans would require testing all these compounds simultaneously at low levels. For example, one chemical might disturb the immune system while other chemicals cause cancerous changes to cells that then go unchecked by immune cells. Chemicals with similar effects, such as oestrogen mimics, together may be strong enough to unbalance hormone metabolism. The few studies that have combined two or more chemicals tend to support this presumption.

The POPs that follow are all toxic in animals. Evidence from low dose-studies varies considerably, but all show effects in animals, and occasional rare human studies, that are of serious concern to human health.

4.4.1 Alkylphenols

These bioaccumulative chemicals are primarily hormone disrupters. Nonylphenol has recently been classified in the EU as a category 3 reproductive toxicant in terms of human fertility and development.

In sewage, alkylphenol ethoxylates degrade into alkylphenols. In the liver, the enzyme P-glycoprotein breaks down and protects organisms from the toxic alkylphenol ethoxylates, but the resulting alkylphenols are oestrogenic (Loo and Clarke, 1998). Octyl- and nonylphenols are the most studied of this group of chemicals.

Both nonylphenol and octylphenol show oestrogenic and anti-androgenic activities (Lee et al., 2003a; Paris et al., 2002). Despite having a lower binding affinity to oestrogen receptors, nonylphenol is a more powerful oestrogen than octylphenol as serum has more of a protective effect against octylphenol. This is an important finding to consider when comparing dietary levels and actual effects of these and other oestrogen mimics (Nagel et al., 1997 and 1999).

Reproductive and Developmental Toxins

Two low-dose developmental studies in rodents provide examples of the effects of alkylphenols on reproduction and development. Sharpe et al. (1995) showed that pre- and postnatal exposure to octylphenols caused a reproducible and consistent decrease in testicular size and daily sperm production in rats during a relatively short period (Table 4.2). A multigenerational mouse study demonstrated that nonylphenol affected both the parents and offspring (Kyselova et al., 2003) with the predominant effects being on the size of male reproductive organs, sperm quality and fertility (Table 4.3).

Immunotoxins

Preliminary studies show that nonylphenol may also disrupt the human immune system. For example, in vitro studies in human breast cells show that nonylphenol inhibits the production of a monocyte chemokine, a chemical which attracts and activates monocytes, an important group of white blood cells (Inadera et al., 2000). In mice, nonylphenol also increases the production of the chemical messenger interleukin-4 (IL-4) in T lymphocytes, and increases levels of IgE antibodies. Both IL-4 and IgE are very important in

Table 4.2
Reproductive effects of 4-octylphenol following prenatal and postnatal exposure via drinking water.

Exposure	Levels (µg/L)[1]	Effects[2]
Postnatal	100	increased body weight increased kidney weight decreased testes weight
Foetal & postnatal	100	decreased kidney weight decreased testes weight decreased prostate weight
Postnatal	1000	decreased testes weight increased kidney weight
Foetal & postnatal	1000	decreased testes weight decreased prostate weight decreased sperm production

[1]Mothers' intake levels of 125mg/kg/day for up to 2 days after birth to 370 mg/kg/day just before weaning for the 1000mg/L group are likely to be overestimates of intake.

[2]Changes to organ weights are all relative to body weight.

(Data from Sharpe et al., 1995)

Table 4.3
Reproductive effects of nonylphenol following multigenerational exposure via drinking water.

Generation	Levels (µg/L)[1]	Effects[2]
Parent male	50	decreased testes weight decreased kidney weight 14% sperm damage
	500	increased epididymis weight 10% sperm damage
Parent female	50	decreased body weight decreased kidney weight
	500	decreased kidney weight
F1 male offspring	50	decreased prostate weight 26% decreased liver weight
	500	increased body weight decreased testes weight 26% decreased liver weight
F2 male offspring	50	decreased litter size
	500	decreased litter size

[1]Actual intake levels not reported.

[2]Changes to organ weights are all relative to body weight.

(Data from Kyselova et al., 2003)

allergy, and nonylphenol may therefore enhance allergic responses (Lee et al., 2003b).

4.4.2 Bisphenol A

Bisphenol A is another EU category 3 reproductive toxicant. Bisphenol A binds to oestrogen receptors range of human cell lines and mimics all the oestrogenicity parameters, confirming it as one of the stronger oestrogenic chemicals (Meerts et al., 2001; Olsen, 2003). In fact, although bisphenol A shows a lower binding affinity than octylphenol *in vitro*, its oestrogenic activity in mice is predicted to be 500 times more powerful due to interactions with serum (Nagel et al., 1997 and 1999).

Bisphenol A follows the classic U-shaped dose curve seen for a range of hormones and hormone mimics. For example, in embryonic cells, low concentrations of bisphenol A increase the development rate while concentrations 100,000 times higher decrease developmental rate (Takai et al., 2000 and 2001). In prostate cancer cells, bisphenol A increases cell proliferation at concentrations 100 times lower than the levels that inhibit cell growth (Wetherill et al., 2002).

Developmental and Reproductive Toxin

The health effects of bisphenol A have been demonstrated in an ever-increasing number of animals studies at levels 2,500 times lower than the EPA's 'lowest observed dose effect' dose. The adverse outcomes range from altered male reproductive organs and aggressive behaviour, to abnormal mammary gland growth, early puberty and reduced breast feeding (Table 4.4). Human infants ingest bisphenol A in formula at an estimated daily rate of 1.6 µg/kg/day, giving little safety margin for doses that cause effects in animals (as little as 2 µg/kg/day) (Houlihan et al., 2003).

Immunotoxin

Various studies show that bisphenol A can also affect the immune system by:

- reducing production of mouse macrophage nitric oxide and tumour necrosis factor-α, a chemical that inhibits tumour growth (Kim & Jeong, 2003).
- inhibiting the production of a monocyte chemokine by human breast cancer cells, a chemical that attracts and activates monocytes (Inadera et al., 2000).

Table 4.4
Assumed safe dose of bisphenol A compared to evidence of low-dose toxicity in rodents.

Effects	Dose (mg/kg/day)	Reference
Assumed safe dose for animals	*5.0*	*US EPA, 1993*
*Assumed safe dose for humans**	*0.05*	*US EPA, 1993*
Effects on vagina	0.100	Schonfelder et al., 2002a
Increased prostate size	0.050	Gupta et al., 2000
Long-term alterations in behavioural patterns in adolescence and adulthood	0.040	Adriani et al., 2003
Abnormal prostate development	0.025	Ramos et al., 2001 Ramos et al., 2003
Abnormal mammary gland growth (changes associated with carcinogenesis).	0.025	Markey et al., 2001
Reduced sperm production	0.020	vom Saal et al., 1998 Sakaue et al., 2001
Early puberty in females	0.020	Honma et al., 2002
Altered maternal care	0.010	Palanza et al., 2002
Early puberty in females	0.0024	Howdeshell et al., 1999
Altered male reproductive glands	0.002	vom Saal et al., 1998
Increased adult prostate weight	0.002	Nagel et al., 1997 Nagel et al., 1999
Reduced testis weight	0.002	Kawai et al., 2003
Decreased antioxidant enzymes in the liver	0.002	Bindhumol et al., 2003
Activated temporary aggressive behaviour	0.002	Kawai et al., 2003

*The oral Reference Dose (RfD) is an estimate of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime.

- enhancing proliferative responses and cytokine production of T lymphocytes (Yamashita et al., 2003)
- increasing IL-4 production in mouse T cells and increasing levels of IgE antibodies levels, both important factors in allergy (Lee et al., 2003b).

Human Studies

The few studies available in humans do link bisphenol A to human health. Serum bisphenol A levels are higher in men as well as in women with polycystic ovary syndrome compared to normal women. These levels correlated with testosterone levels indicating that there may be differences in androgen-related metabolism of bisphenol A (Takeuchi & Tsutsumi, 2002). This is a factor to consider when comparing exposure levels to possible health effects.

Bisphenol A has also been found in ovarian follicular fluid of women requiring IVF treatment (Ikezuki et al., 2002). Mothers carrying foetuses with abnormal chromosomes had higher serum bisphenol A concentrations than those with normal foetuses (Yamada et al., 2002).

Concentrations of bisphenol A have been found at levels five times higher in amniotic fluid at 15–18 weeks gestation than in other fluids (Ikezuki et al., 2002). This is a vital period of organ development and highlights the increased exposure and susceptibility of the developing foetus to chemicals that contaminate pregnant women.

4.4.3 Brominated Flame Retardants

Most brominated flame retardants (BFRs) are persistent and/or bioaccumulative and several are endocrine disrupters. They are widespread as far as the Arctic where their concentrations in seals are increasing exponentially (Ikonomou et al., 2002).

Toxicity data on BFRs are severely limited and focus primarily on high dose studies of PBDEs in animals. The toxic profile of the PBDEs is proving to be very similar to PCBs. Their toxicity includes birth defects, liver and kidney damage, thyroid imbalances and neurological damage to animals and humans. Generally, the penta-BDEs seem to be the most toxic (Darnerud et al., 2001; Darnerud, 2003).

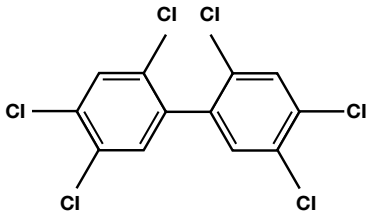
Data on TBBP-A and HBCD are almost completely lacking. TBBP-A *in vitro* studies indicate toxic effects on the immune system and thyroid, while HBCD seems to affect the liver and thyroid (Darnerud et al., 2001; Darnerud, 2003).

Thyroid Toxins

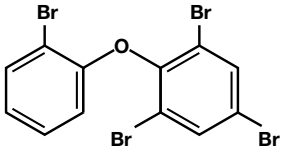
The similarity of PBDEs to PCBs and the thyroid hormone may underlie their toxicity: PCBs, PBDEs and thyroid hormones all consist of two six-carbon rings decorated with halogens of chlorine, bromine or iodine respectively (Fig. 4.1). *In vitro* studies show that PBDE metabolites, as well as pentabromophenol (PBP) and TBBP-A, compete strongly with the thyroid hormone, thyroxin, for binding to the thyroxin serum binding protein, transthyretin (Meerts et al., 2000). It is likely that in the body, PBDEs and their metabolites displace thyroid hormones from transthyretin thereby allowing increased metabolism of the hormone and thus decreased levels in serum. The authors speculate that the effects of BFRs on the thyroid *in vivo* may be comparable to the thyroid-disrupting effects of PCBs (Meerts et al., 2000). As the development of the central nervous system is highly dependent on thyroid hormones, alterations in thyroid homeostasis may result in permanent neurobehavioral defects.

Figure 4.1
The structural similarity of the brominated flame retardants, polybrominated diphenyl ethers (PBDEs), to the polychlorinated bisphenols (PCBs) and thyroid hormones may underlie their toxicity.

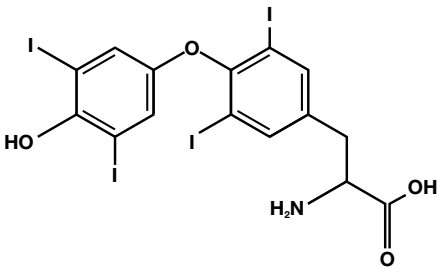
2,2',4,4',5,5'-hexachlorobiphenyl (PCB-153)



2,2',4,4',6-pentabromo diphenylether (BDE-100)



Thyroxine (T4)



Neurotoxins

PBDEs, such as BDE-209, can be taken up during neonatal life, distributed throughout the body and concentrate in the brain. They induce developmental neurotoxic effects in adult mice that worsen with age and lead to abnormal behaviour. The effects seem to be inducible only during a defined critical period of neonatal life (Viberg et al., 2003). For example, perinatal exposure to PBDEs at levels from 0.6 mg/kg produced several behavioural alterations in mice with the main

effect being marked hyperactivity at adulthood (Branchi et al., 2002 and 2003). Learning and memory deficits have also been found at adulthood for neonatally exposed animals (Eriksson et al., 2001). A recent study shows that HBCD also has behavioural effects on neonatal mice at 0.9 mg/kg (cited in Darnerud, 2003).

A rat study showed that HBCD and TBBP-A inhibit the uptake of the neurotransmitters dopamine, glutamate and gamma-amino-n-butyric acid (GABA) by neurones at a concentration level similar to those found with studies on PCBs and ecstasy (Mariussen & Fonnum, 2003).

Oestrogenic Effects

A range of PBDEs and brominated bisphenol A compounds, such as TBBP-A, show oestrogenicity in human cells lines and bind to the oestrogen receptors (Meerts et al., 2001). The metabolism of PBDEs to hydroxylated-PBDEs produce more potent oestrogen mimics. Brominated bisphenol A compounds with the lowest bromination showed the highest effect, and among the PBDEs, BDE-100, BDE-75 and BDE-51 showed the highest activity. TBBP-A does not mimic all the oestrogen test parameters and, therefore, could cause an unbalanced oestrogen response (Olsen et al., 2003).

Cancer Promoters

Three PBDEs (mono-, di-, and tetra-BDE) induce intragenic genetic recombination in mammalian cells, which is known to provoke a number of diseases, including cancer (Helleday et al., 1999). Tris(2,3-dibromopropyl)phosphate and its metabolite 2-bromoacrolein may be clastogens – chemicals which cause breakage in chromosomes (van Beerendonk et al., 1994).

4.4.4 Organotins

Organotins are persistent chemicals that accumulate throughout the body, primarily in the liver and kidneys. The tri-tins, such as TBT and TPT, are all listed as poisons and described as respiratory toxins, fetotoxins, reproductive toxins, immunotoxins, possible carcinogens, skin and respiratory irritants, and allergens (Norris, 1994; van Heijst, 1994).

The toxicity of organotins stems primarily from the fact that they are powerful metabolic inhibitors. They inhibit a range of enzymes responsible for the metabolism, signalling, and regulation of many cell activities. This can cause a variety of effects at various concentrations depending on the target organ. (Norris, 1994).

Reproductive and Developmental Toxins

Organotins are well-known hormone disrupters with devastating effects on marine molluscs. TBT and TPT inhibit a variety of enzymes responsible for the production of male and female sex steroid hormones – oestogens, testosterone, and oestradiol (Doering et al., 2002; Lo et al., 2003; Steckelbroek et al., 2001). While low-dose developmental studies are lacking in mammals, insufficient activation of male hormones is known to be responsible for developmental disorders of the male reproductive tract.

A recent study suggests that organotins may also cause developmental effects *in utero* at relatively low doses by targeting the maternal thyroid (Adeeko et al., 2003). Effects varied depending on dosage but appeared to be linked to the reduction of maternal serum thyroxine and triiodothyronine throughout gestation. Effects included reduced maternal weight gain; increased post-implantation loss; decreased litter sizes; decreased foetal weights; delayed foetal skeletal development; and abnormalities in genital development in male fetuses.

Immunotoxins

Organotins are well known immunotoxins which target a range of white blood cells and destroy or limit their ability to function. For example:

- DBT and TBT both suppress mitogenesis in human lymphocytes. This process of stimulating lymphocytes to undergo mitosis is vital for the reproduction of lymphocytes during the immune response to invasion by organisms such as bacteria or viruses (Nakata et al., 2002).
- TBT causes apoptosis (or self-destruction) of human T lymphocytes (Stridh et al., 2001).
- BPT, TBT and TPT all inhibit the cytotoxic function of human NK cells, which are responsible for killing tumour cells and cells that are infected by viruses (Whalen & Loganathan, 2001; Whalen et al., 2002a and b; Whalen et al., 2003).
- TPT enhances neutrophil maturation (Watanabe et al., 2003). It also inhibits superoxide production by human neutrophils, which thereby limits the ability of neutrophils to kill bacteria (Miura & Matsui, 1991).

Cancer Promoters

TPT is a potent spindle poison – a toxin that interferes with the cell components responsible for moving chromosomes into place before a cell divides. TPT acts synergistically with pentachlorobiphenyl, a PCB, to induce abnormal chromosome arrangements in mitosis at very low concentrations (10nM and 50nM) (Jensen et al., 2000).

4.4.5 Phthalates

Toxicity studies primarily focus on DEHP, the most toxic phthalate, and DINP, and the application of these profiles to humans remain controversial (CDC, 2003; Lovekamp-Swan & Davis, 2003; Shea, 2003).

Phthalates are hormone disrupters that act as anti-androgens. The diester forms of phthalates are converted to monoester forms in the gut, liver and blood. These are considered the ultimate toxins, and the length and structure of the side chain is important for their levels of toxicity (Lovekamp-Swan & Davis, 2003).

The primary mechanism of toxicity of phthalates appears to be via the activation of a set of proteins called PPARs – nuclear transcription proteins that regulate a wide variety of cell activities (Boiter et al., 2003; Lovekamp-Swan & Davis, 2003). PPARα is found in tissues that are highly metabolically active, such as the liver. Activation of PPARα by DEHP/MEHP results in decreased transcription of aromatase, the enzyme which converts testosterone to estradiol, and therefore disrupts sex hormone metabolism. PPARγ is highly expressed in various human tissues including adipose tissue and immune cells. PPARγ is a key regulator of cell differentiation. By activating PPARγ, DEHP/MEHP disrupts, for example, the critical growth and differentiation of the ovarian follicle.

Phthalates also have toxic effects that are at least partly independent of PPAR activation. Testicular toxicity is partly caused by interference with binding of follicle stimulating hormone to its receptor on Sertolli cells (Boiter et al., 2003). Phthalates may also bind to the oestrogen receptor. For example, the effects of 19 phthalates in human breast cancer cells (Okubo et al., 2003) showed that:

- DCHP, DEHP and BBP are oestrogenic
- DCHP, MOP and MEHP are cytotoxic
- MMP, MCHP, MBZP and MIPrP are anti-oestrogenic.

Reproductive and Developmental Toxins

Phthalates, following their conversion to a toxic metabolite, can produce foetal death, malformations, and reproductive toxicity, with different profiles for each phthalate and different potencies (Shea, 2003).

Maternal exposure of rodents to DEHP/MEHP, causes reduced embryonic implantation; increased resorptions; skeletal, cardiovascular and eye abnormalities; neural tube defects; intrauterine death; increased postnatal death; and decreased intrauterine and postnatal growth in rodent

pups (Gray, 2000; Moore et al., 2001; Shea, 2003). Foetal toxicity can occur without evidence of maternal toxicity. The immature male reproductive tract is the most sensitive system. Pathological changes in the testis, and decreased sperm numbers are consistent effects. Prenatal and postnatal exposure leads to complete female infertility and decreased male fertility. Sertoli cells in the testicle and the granulosa cells of pre-ovulatory follicles in the ovary appear to be the primary cellular target of DEHP/MEHP.

Other phthalates appear to have a similar pattern of toxicity but at higher doses. For example:

- DINP causes skeletal and genito-urinary abnormalities (Shea, 2003).
- DBP is a testicular toxicant and causes reproductive tract malformations in male rats after *in utero* exposure (Lovekamp-Swan & Davis, 2003).
- Maternal exposure to low doses of BBP (125–370 µg/kg/day) lead to decreased testes weight in male offspring following prenatal and postnatal exposure (Sharpe et al., 1995).
- DPP and DHP cause testicular atrophy and are both female and male reproductive toxicants (Lovekamp-Swan & Davis, 2003; Shea, 2003).

Cancer Promoters

The carcinogenic effects of DEHP in liver are thought to be due to PPARα activation (Lovekamp-Swan & Davis, 2003). Humans have one-tenth the level of PPARα expression in liver compared to mice so the carcinogenicity in humans is under dispute. The activation of enzymes by PPARα may also increase susceptibility to other chemicals whose metabolites are toxic, including carcinogens.

PPARγ plays a critical role in adipocyte differentiation, therefore DEHP activation of PPARγ in tissues other than liver could alter normal pathways of differentiation. This could explain the teratogenic effects of DEHP as development is a critical time for differentiation, and suggests that it could also play a role in cancers (Lovekamp-Swan & Davis, 2003).

Immunotoxins

There is some evidence of immunotoxicity which may be related to PPARγ on immune cells. PPARγ activation profoundly alters the immune properties of these cells, usually leading to the inhibition of immune responses (Nencioni et al., 2003). For example, phthalates can disrupt normal antibody production. In one study, various phthalate metabolites either stimulated or suppressed IgG and IgE antibody produc-

Table 4.5
Different phthalate metabolites can both stimulate and suppress antibody production depending on their concentration levels (µg/mL).

Phthalate Metabolite	Decreased Antibody Production		Increased Antibody Production	
	IgE	IgG1	IgE	IgG1
MBnP	ns	ns	ns	ns
MEHP	1000	1000	10	ns
MiDP	100	100	ns	ns
MiNP	1000	10	100	ns
MnBP	ns	ns	ns	ns
MnOP	1000	1000	ns	10 and 100

IgG1: Immunoglobin G1; IgE: Immunoglobin E; MBnP: monobenzylphthalate; MEHP: mono-2-ethylhexyl phthalate; MiDP: mono-iso-decylphthalate; MiNP: mono-iso-nonylphthalate; MnBP: mono-n-butylphthalate; MnOP: mono-n-octylphthalate; NS: no significant effect.

(Data from Larsen et al., 2001)

tion depending on their concentration levels (Larsen et al., 2001). Interestingly, MEHP induced IgE production at relatively low levels – the antibody responsible for allergic reactions (Table 4.5).

Human Studies

An interesting study in Puerto Rico demonstrated a link between the increasing incidence of premature breast development (thelarche) and exposure to phthalates (Colon et al., 2000). The annual incidence of thelarche in Puerto Rican girls aged 6–24 months was 8 cases per 1000 female births from 1984–1993, the highest ever reported. High levels of phthalates were detected in 68% of all thelarche girls but only 17% of normal girls. The authors suggest that the high incidence of thelarche in Puerto Rico may be caused by a high exposure to phthalates due to high importation of plastic packaged foods, with a year-round high temperature and humidity which promotes closed environments and frequent use of air-conditioners.

Women with endometriosis have a higher level of DEHP in their blood than normal women, and 92.6% of these also had detectable DEHP and/or the metabolite MEHP in their peritoneal fluid (see Table 2.5, Section 2). This suggests that DEHP plays a role in the pathogenesis of endometriosis (Corbellis et al., 2003).

Chewing on plastics that contain phthalates may increase the risk of developing tumours in the mouth, and upper airway and digestive tracts, according to one study, which showed that DBP and DiBP cause significant DNA damage to human tonsils *in vitro* (Kleinsasser et al., 2001).

Patients exposed to DEHP as the consequence of medial treatment with devices containing PVC may provide evidence of the human toxicity of phthalates. Virtually all medical devices made from PVC contain DEHP. Patients on dialysis, blood transfusions, artificial ventilation, and exchange transfusions are at risk. Premature infants are particularly at risk as they are exposed to relatively high amounts of DEHP while in intensive care. Reports of possible links between DEHP and disease in humans include (EC, 2002):

- development of polycystic kidney disease in haemodialysis patients
- pulmonary toxicity in mechanically ventilated pre-term infants with PVC tubes
- cholestasis (bile flow stops) in infants with serum levels of 18–98 µg/mL DEHP following the use of an artificial lung (extracorporeal membrane oxygenation therapy)
- abnormalities in livers in patients after a year of haemodialysis
- liver toxicity in Rhesus monkeys receiving blood plasma from PVC bags over a year.

As described in Section 4.2.4, extremely low birth weight (ELBW) infants are 100 times more likely to develop the liver tumour hepatoblastoma. While ELBW infants may develop this tumour anyway, exposure to high levels of DEHP while in intensive care may also play a role in its development (EC, 2002).

4.4.6 Artificial Musks

Artificial musks are persistent and bioaccumulative chemicals. Most health studies focus on musk xylene (MX) and musk ketone (MK).

Although MX and MK are structurally similar and possess almost identical physico-chemical properties, they differ significantly in their biological properties. Both musks possess oestrogenic activity *in vitro* with MK showing an affinity for the oestrogen receptor three times greater than MX (Bitsch et al., 2002). However, when MK is reduced to its metabolite it loses its activity, whereas when MX is converted to p-amino-musk xylene, its oestrogenic potency increases (Bitsch et al., 2002).

MX appears to have a higher half-life in humans than rodents, and induces the liver CYP 2B enzymes in rat and mice (which its metabolite then inhibits) (Schmeiser et al., 2001). MX has been detected chemically bound to haemoglobin (Hb-adducts) in the blood of ten volunteers (Riedel et al., 1999). The ability to form Hb-adducts correlates well with the formation of DNA adducts which cause tumours, suggesting a cancer risk for substances causing Hb-adducts. Chronic exposure to MX is also known to cause mouse liver tumours (Schmeiser et al., 2001).

Few toxicological studies on MK are available. However, it shows a strong induction of liver enzyme activities in rats which are distinct from those inhibited by MX (CYP 1A1 and 2, and CYP 2B). These liver enzymes metabolise a range of chemicals and drugs, turning some of them, such as polycyclic aromatic hydrocarbons, into carcinogens and mutagens. Exposure of humans to MK might increase their susceptibility to the hazards of other cancer-causing chemicals. For example, MK acts as a co-genotoxicant by amplifying the DNA damaging effects of the polycyclic aromatic hydrocarbon, benzo(a)pyrene, in human cells at relatively low doses (Mersch-Sundermann et al., 2001).

The polycyclic musks, AHTN and HHCB, are selective oestrogen receptor modulators, and induce both oestrogenic and anti-oestrogenic activity depending on the cell type and the receptor subtype targeted. Weak oestrogenic effects are observed at relatively high concentrations (10 µM) while anti-oestrogenic effects are seen at 0.1 µM (Schreurs et al., 2002).

One human study has shown a significant association between MX and MK levels in blood and hormonal and gynaecological problems in women suggesting that these musks cause reproductive toxicity and endocrine effects in humans (Eisenhardt et al., 2001).

4.4.7 Chlorinated Paraffins

Chlorinated paraffins (CPs) are persistent and bioaccumulative; however, there is very little data available on low-dose chronic effects in animals, and none available on their effects in humans. The data available suggests that theses chemicals may act as carcinogens and disrupt thyroid hormones in humans.

The toxicity of two CPs are fairly well characterised: C12 60% and C23 43%. The C12 60% appears to have a greater potential for chronic toxicity and carcinogenicity than C23 43%. The C12 60% is toxic to liver, lymph glands, kidney, and thyroid; causes benign tumours in kidney, liver, and thyroid; and causes malignancies in kidney, and leukaemia. C23 43% is associated with malignant lymphomas (Bucher et al., 1987; NTP, 1986a; NTP, 1986b).

Short and intermediate, but not long carbon chain CPs, are potent inhibitors of intercellular communication, which may be their mechanism for promoting tumours (Kato & Kenne, 1996; Warngard et al., 1996).

One study has shown that low levels (50 mg/kg) of medium length CPs (C14–17, 52%) are toxic to liver and thyroid in female rats (Poon et al., 1995). A rare study looking at the affects of two chemicals (at mg/kg levels) on thyroid health demonstrated a synergistic effect between the flame retardant BDE-47 and the CP known commercially as 'Witaclor 171P' in decreasing free plasma thyroxine in rats (Hallgren & Darnerud, 2002).

5 CONCLUSION

While this report was not intended to be a comprehensive literature review, it does provide ample evidence that:

- Many POPs are now being discovered in human tissues, including breast milk, and the blood of foetuses and newborn children (for a summary see Table 5.1). Given the wide range of everyday products containing these POPs and their contamination of the environment, it is likely that further evidence of contamination is forthcoming.
- Unborn and newborn children are particularly at risk of exposure to POPs as they absorb chemicals more efficiently, process them more slowly and eliminate them less efficiently.
- There are a number of non-infectious diseases on the rise, particularly in industrial countries. These include congenital defects, immune diseases, developmental and reproductive disorders, neurological disorders and cancers. These diseases often begin in childhood, and may be caused by damage to the developing child – the period of life most susceptible to chemical damage.
- While the causes of these diseases are not clear, there is a general concern within the scientific and medical communities that chemicals are contributing to an increase in these diseases.
- The laboratory evidence of toxicity varies widely for each group of POPs, but there is increasing evidence that low doses of these chemicals are linked with a broad range of health effects that were previously unexplored in high-dose studies.
- Direct evidence of the effects of POPs on human health is lacking.

It is clear that the 'evidence' generally regarded as proof of harm to human health is not available for POPs, and even with further research is unlikely to be. Strong links between POPs and disease are very difficult to establish: there are no uncontaminated control groups for comparison; many of these diseases do not become apparent until long after chemical exposure begins; actual exposure levels are very difficult to estimate and are likely to vary considerably from person to person and over an individual's lifetime; and very little is known about the effects of exposure to chemical mixtures.

Waiting for further 'solid' evidence of chemical effects on health will mean risking irreversible damage to the health of further generations of children.

Continued research into the health effects of POPs is certainly required in order to better understand the causes of non-infectious diseases and, hopefully, to monitor their decline as these POPs are removed from products or substituted with safer alternatives. This may be the best evidence of their effects on health we can provide.

Table 5.1
Summary of the possible health effects of the chemical contamination of the child.

Chemical group and examples	Found in	Laboratory evidence	Human evidence	Likely effects on child health
Alkylphenols Octylphenol Nonylphenol	Umbilical cords Breast milk	Oestrogen mimics Immunotoxins		Developmental & reproductive disorders Immune disorders
Bisphenol A	Umbilical cords Umbilical cord blood Amniotic fluid Placental tissue Breast milk Adult ovaries Adult blood	Oestrogen mimic Immunotoxin	Linked to polycystic ovary syndrome, female fertility problems, & abnormal foetal chromosomes.	Developmental & reproductive disorders Immune disorders
Brominated flame retardants PBDEs TBBP-A HBCD	Umbilical cord blood Breast milk Breast fat Adult blood Adult fat	Thyroid hormone disrupters Oestrogen mimics Neurotoxins Cancer promoters		Developmental & reproductive disorders Nervous system disorders Cancers
Organotins Dibutyltin Tributyltin Triphenyltin	Adult blood Adult liver	Enzyme inhibitors Hormone disrupters Immunotoxins Cancer promoters		Developmental & reproductive disorders Immune disorders Cancers
Phthalates DEHP DINP	Child blood & urine Adult blood & urine	Enzyme disrupters Hormone disrupters Immunotoxins Cancer promoters	Linked to premature breast development & endometriosis. DEHP in medical devices linked to liver, kidney & respiratory diseases.	Developmental & reproductive disorders Immune disorders Cancers
Artificial musks Musk xylene Musk ketone AHTN HHCB	Breast milk Adult blood Adult fat	Enzyme inducers Hormone disrupters	Linked to hormonal & gynaecological problems in women	Developmental & reproductive disorders Cancers
Chlorinated paraffins C12 60% C23 43%	Adult fat	Inhibit intercellular communication Toxic to liver, kidney, thyroid, & lymph glands Cancer promoters		Cancers

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